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Antimycobacterial Agents

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Antimycobacterial Agents

- **Those are drugs used for treatment of diseases caused by mycobacteria**
- **Mycobacteria is a genus of Gm+ve acid-fast bacilli belonging to mycobacteriaceae; e.g.**

- Tuberculosis, **- Leprosy.**

Tuberculosis (TB)

- **TB is a chronic bacterial infection, caused by *Mycobacterium Tuberculosis*.**

- **Resurgence in Tuberculosis (TB)**

- **Spread of HIV**
- **Increase in homeless population and poor without adequate health care**
- **Decreased funding for TB prevention and treatment programs**

- **Challenges in Treating Tuberculosis**

- **Chronic infection**
- **Organisms are frequently intracellular**
- **Organisms exhibit periods of metabolic inactivity**
- **Resistance to drug therapy**

Antitubercular Drugs

- **There are diverse of compounds that combat *M.Tuberculosis* organism, such as:**

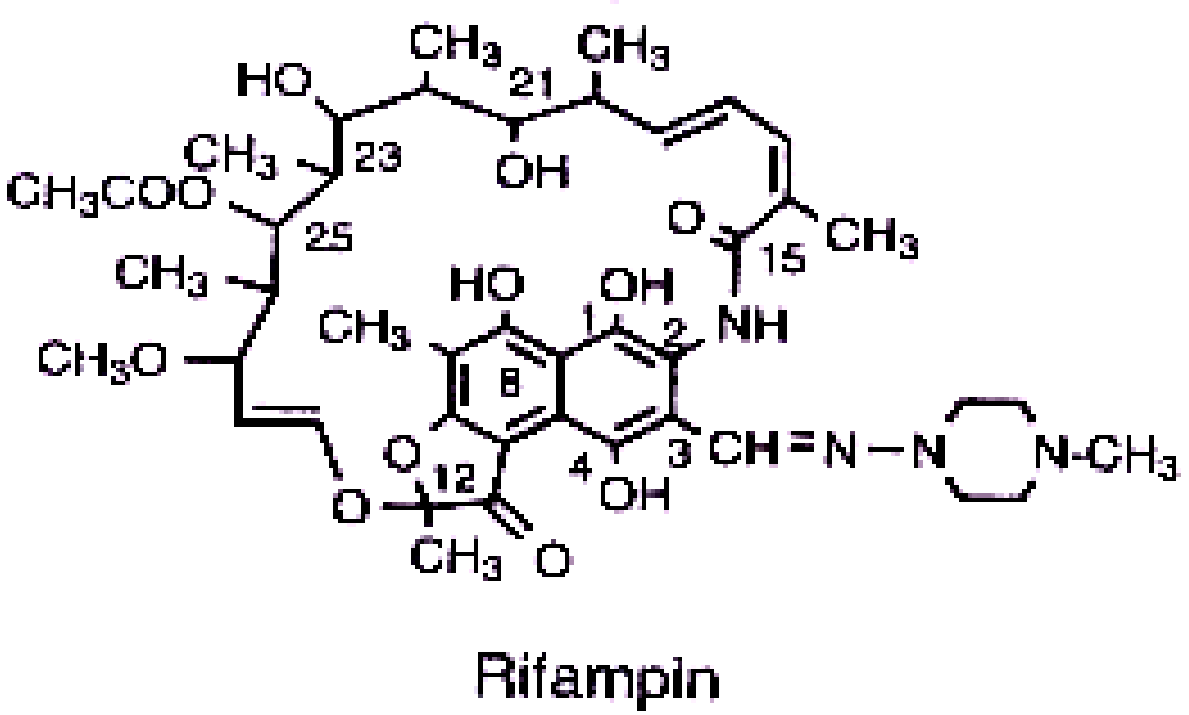
1. **Antibiotics: Rifampicin and Streptomycin;**
2. **Hydrazides: Isoniazid (INH);**
3. **Amides: Pyrazinamide;**
4. **Aliphatic diamines: Ethambutol.**

- **First Line of treatment:**
  - **Isoniazid (INH), Rifampin are the most effective and have lowest toxicity.**
  - **Ethambutol, Streptomycin are less effective and more toxic agents.**
  - **p.Amino salicylic acid (Not available anymore).**
- **Second Line of treatment:**
  - **Those are the least effective and the most toxic.**
  - **Ciprofloxacin or Ofloxacin, Amikacin, Kanamycin, Cycloserine .**

Treatment (Multidrug therapy)

- **Isoniazid, Rifampin & Ethambutol are given for 2 months.**
- **Isoniazid & Rifampin are given for 4 months.**
- **In case of drug resistance to isoniazid a combination of Isoniazid, Ethambutol, Rifampin & Pyrazinamide should be used.**
- **Incidence of drug resistance is 2-5%.**

1- Rifampin (Rifampicin, Rifadin)



Rifampin

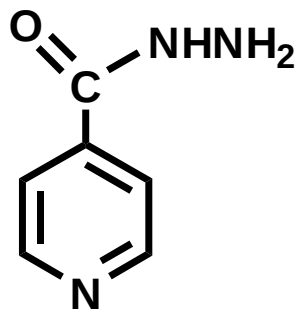
- **Rifampin (RIF) is a semisynthetic agent prepared from rifamycin B, (an antibiotic isolated from streptomyces mediterranei).**
- **Rifampin as a derivative of rifamycin B gains the advantage of being**
  - **Oraly active as a broad spectrum antibiotic**
  - **Highly effective against a variety of gram-ve and gram+ve organisms,**
  - **High clinical efficacy in the treatment of TB.**

- **Uses**
  - **Tuberculosis**
  - **Leprosy**
  - ***Haemophilus influenzae***
- **Adverse effects**
  - **Hepatitis (hepatotoxicity).**
  - **Discoloration of body fluids.**
- **Drug Interactions**
  - **Induces cytochrome P450 enzymes.**
  - **Decreased levels of zidovudine, Benzodiazepines, Barbituraes, Warfarin.**

Rifampin Mode of Action:

- **Rifampin inhibits bacterial DNA-dependent RNA polymerase (DDRP).**
- **Inhibition of DDRP leads to blocking of chain formation in RNA synthesis.**
- **It has been suggested that the naphthalene ring of RIF binds to an aromatic amino acid in the DDRP protein.**

2- Isonicotinic hydrazide, Isoniazid (INH)



Isoniazid

- Isoniazid is a synthetic antibacterial agent with bactericidal activity against M. tuberculosis.
- Considered to be the drug of choice in TB chemotherapy.

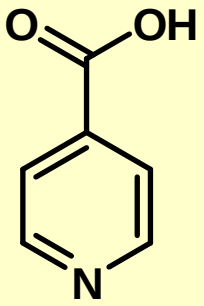
INH-Activity:

- **Bactericidal to actively dividing cells i.e. growing bacilli.**
- **Bacteriostatic to the resting or dormant strains, i.e. resting bacilli,**
- **Resistant strains do develop when INH used alone.**
- **Therefore, combination therapy is the preferred line of treatment forTB.**

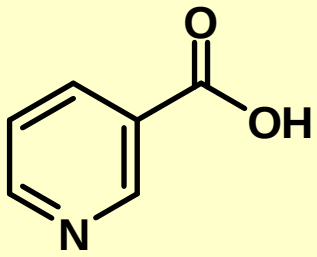
Mode of action:

Unknown, but the hypothesis includes different proposed mechanisms: -

- **Inhibition of mycolic acids biosynthesis which are part of cell wall structure.**
- **INH is activated through an oxidation reaction to isonicotinic acid, which in turn acts as antimetabolite of nicotinic acid. It replaces nicotinic acid incorporation into NAD, which will be then unable to catalyze normal oxidation/reduction reactions.**

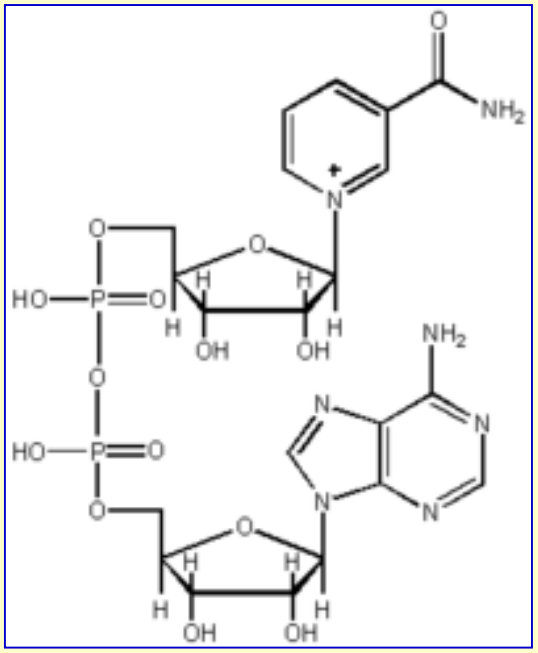


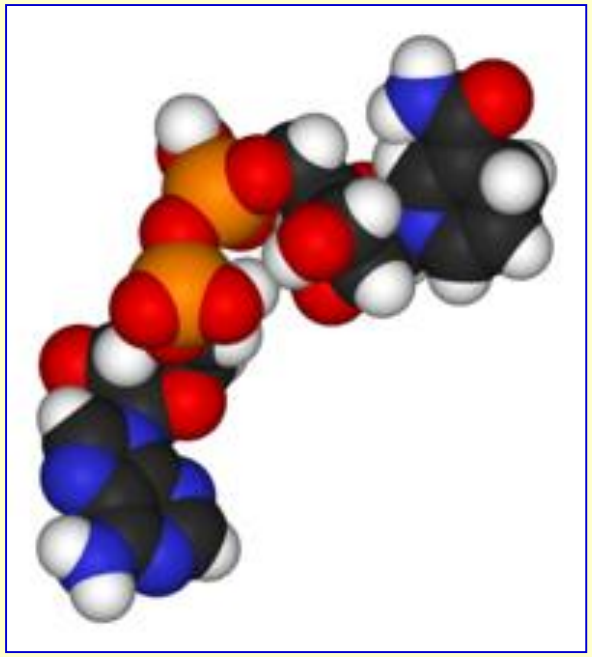
Isonicotinic acid



Nicotinic acid

- **Interference with NAD+ conversion to NADH hence affects the electron transport system.**





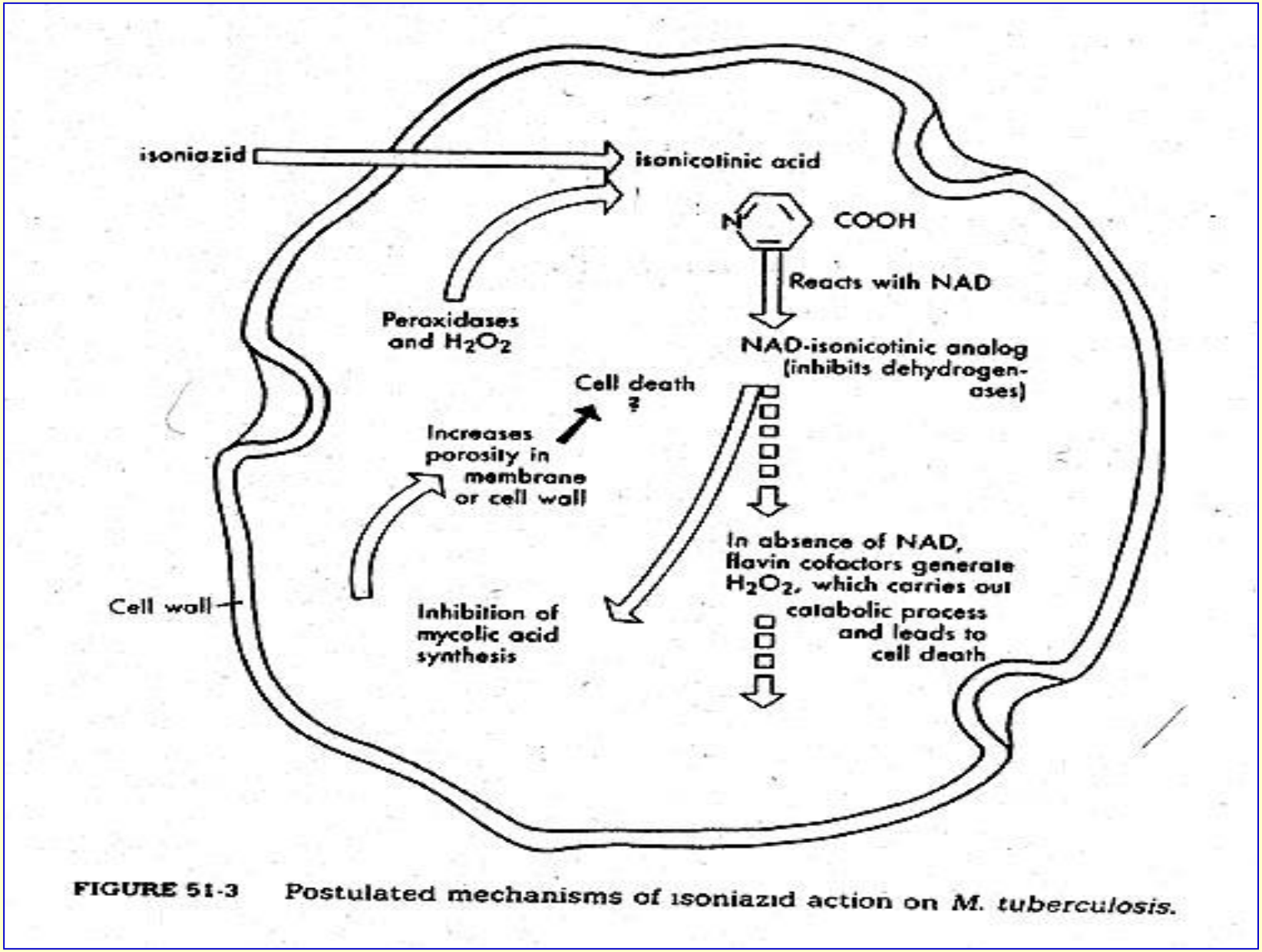
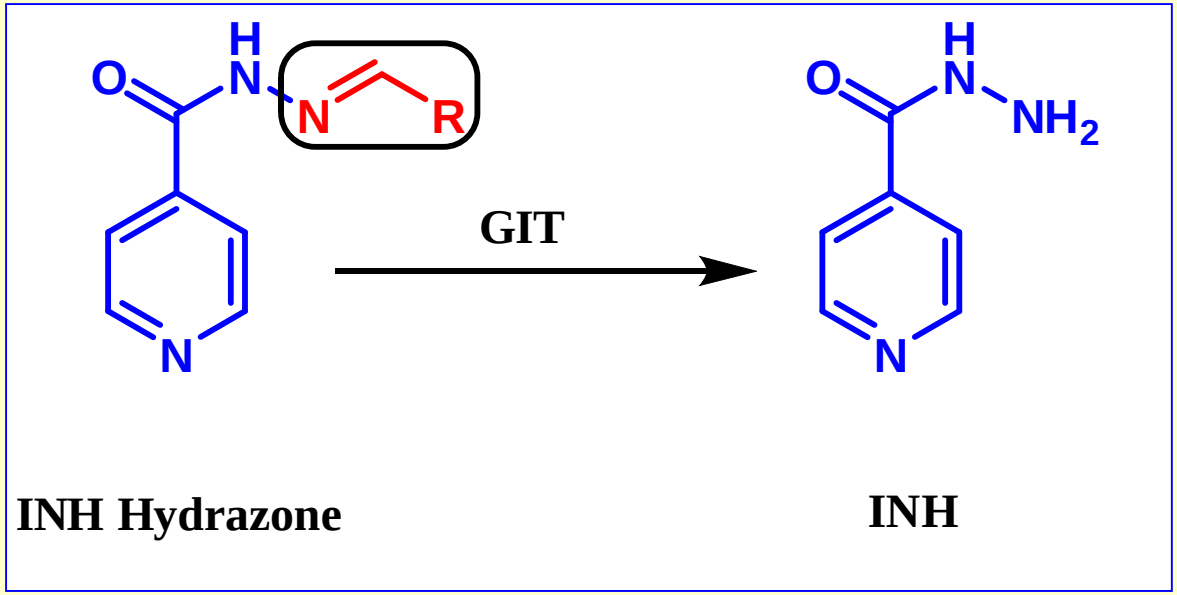


FIGURE 51-3 Postulated mechanisms of isoniazid action on *M. tuberculosis*.

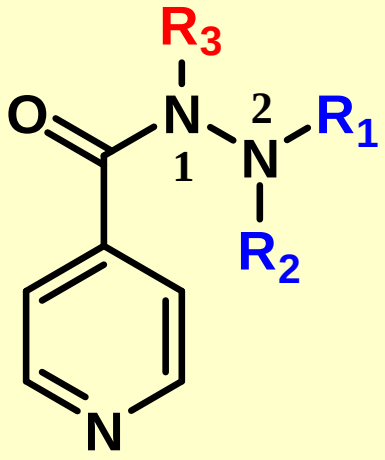
Structure Activity Relationship (SAR) of INH:

(1) Isonicotinic acid derivatives such as isoniazide hydrazones found to possess tuberculostatic activity but they are unstable in GIT, releasing the active INH (Dose Alert is in effect).

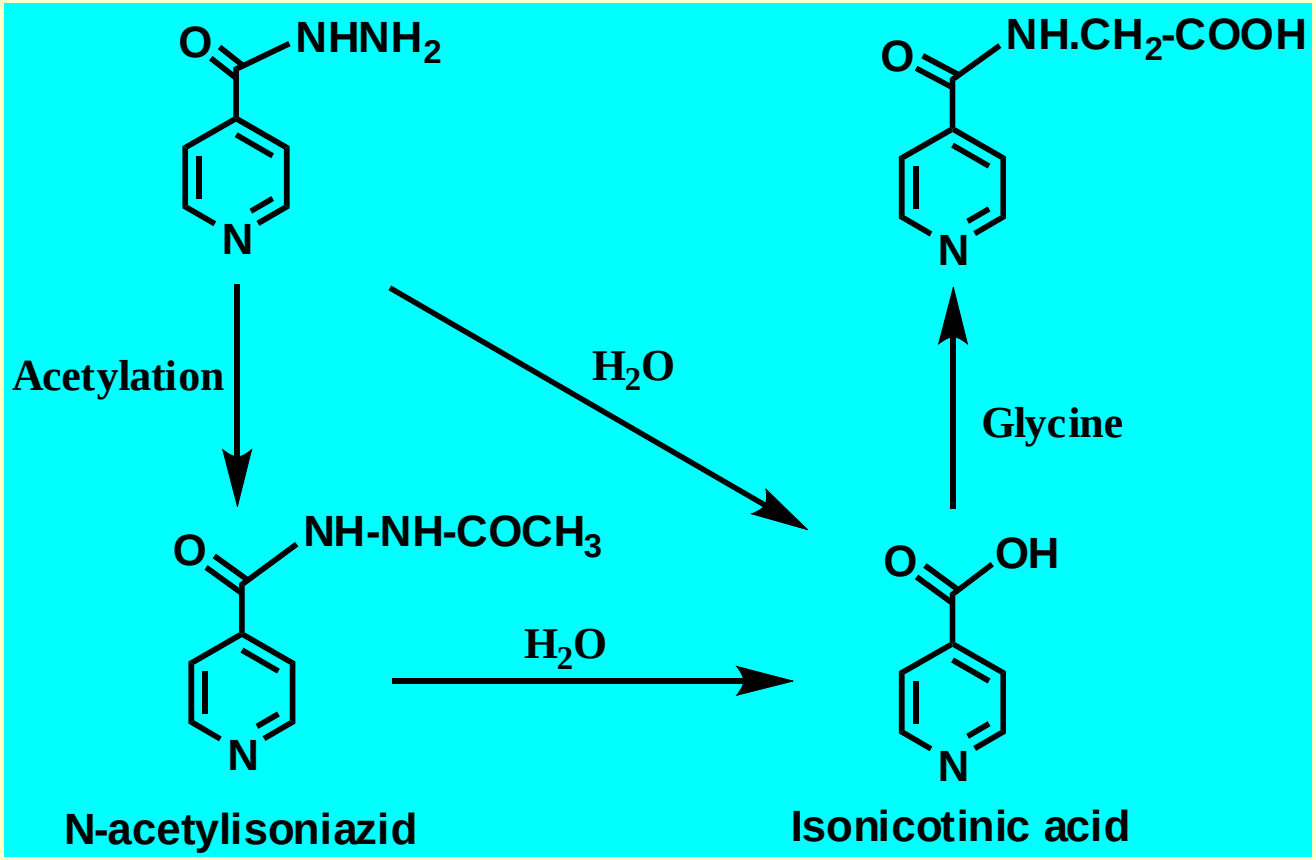


(2) Substitution of the hydrazine portion of INH with alkyl groups resulted in series of active and inactive derivatives:

- **Substitution of N^2 position resulted in active compounds (R1, R2 = alkyl; R3=H) e.g Iproniazid.**
- **whereas any substitution of N^1 eliminate the activity (R1, R2 = H; R3= alkyl).**

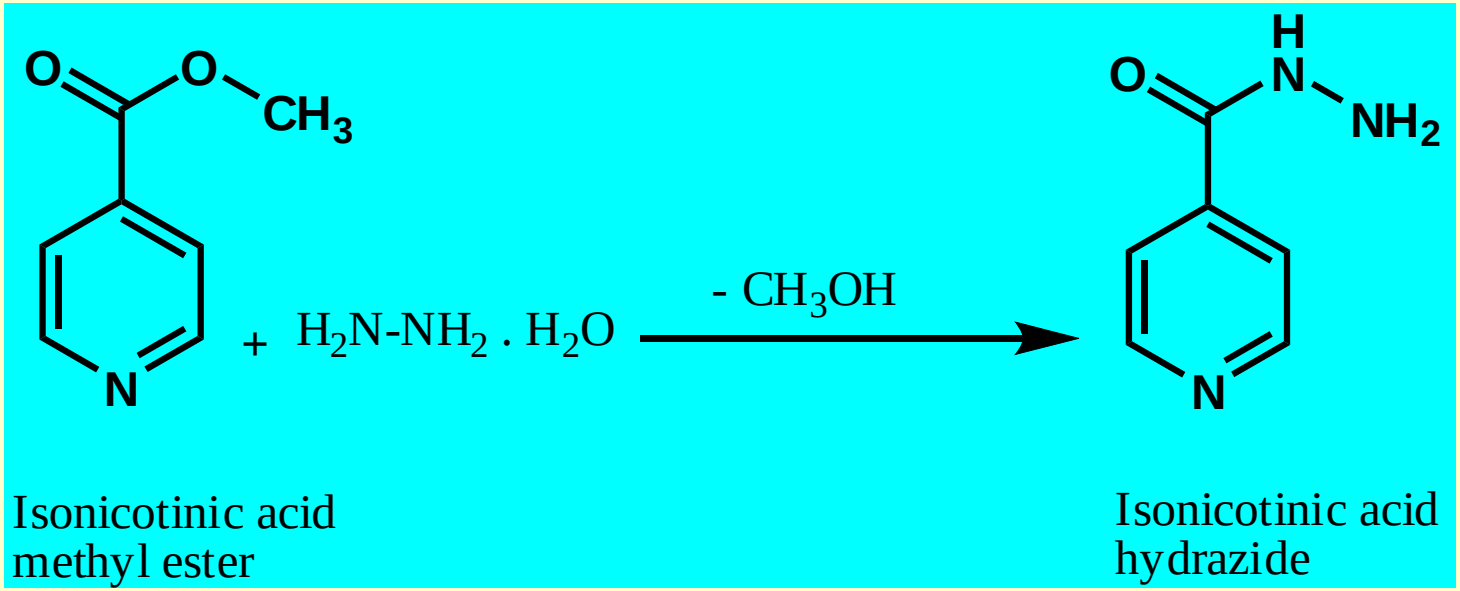


INH-Metabolic pathways:

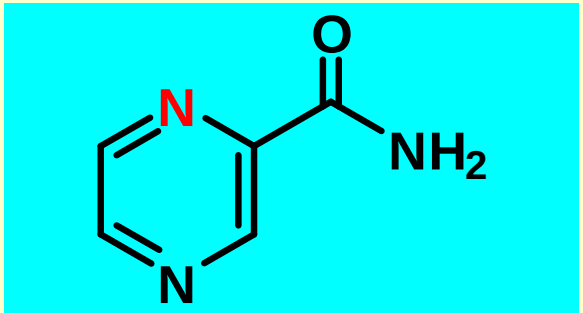


- **INH is extensively metabolized in liver and small intestine into the inactive metabolite N-acetylisoniazid.**
- **The enzyme responsible for such acetylation is N-acetyltransferase.**
- **Individuals with high concentrations of the enzyme are referred to as rapid (fast) acetylators, this will result in a need to adjust the dosage.**
- **Other metabolites include isonicotinic acid, which is found in the urine as a glycine conjugate. Isonicotinic acid may also result from hydrolysis of acetylisoniazid;**

Synthesis of INH:



3- Pyrazinamide (PZA)

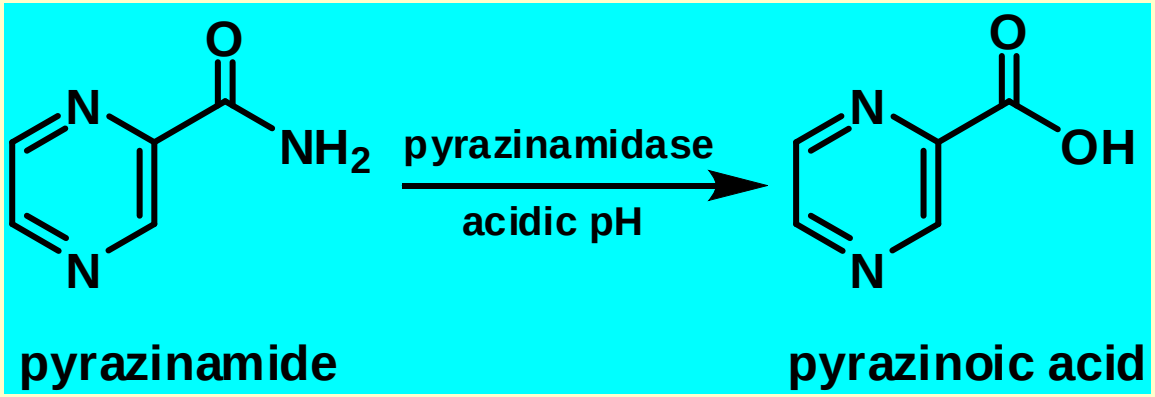


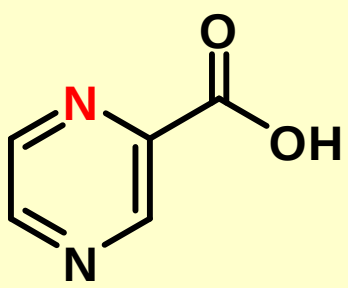
Pyrazine-2-carboxamide

- **Pyrazinamide is a bioisostere of nicotinamide and possess bactericidal effect against *M. tuberculosis*.**
- **Despite the fact that resistance develops quickly to this agent, combination therapy has proven an effective means of reducing the rate of resistant strain development.**
- **PZA causes liver toxicity!**

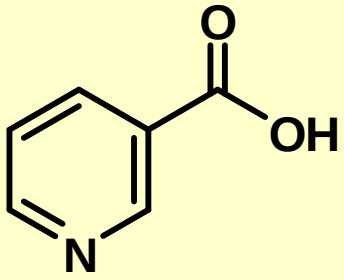
Mode of action:

- **Pyrazinamide is a prodrug that stops the growth of *M. tuberculosis* .**
- **M. tuberculosis produce pyrazinamidase enzyme which is only active at acidic pH.**
- **Pyrazinamidase converts pyrazinamide to the active form, pyrazinoic acid, which inhibits fatty acid synthetase I enzyme, required for fatty acids synthesis.**

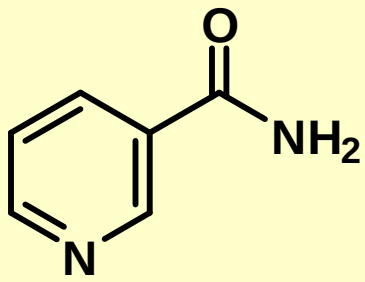




pyrazinoic acid



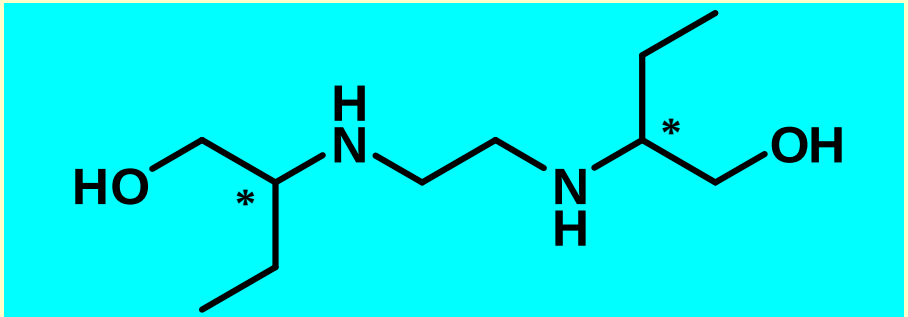
Nicotinic acid



Nicotinamide

- **structural similarity between pyrazinoic acid and nicotinamide suggests that pyrazinoic acid function as nicotinamide antimetabolite and thus, interferes with NAD synthesis .**
- **Mutations of the pyrazinamidase gene (*pncA*) are responsible for pyrazinamide resistance in *M. tuberculosis*.**

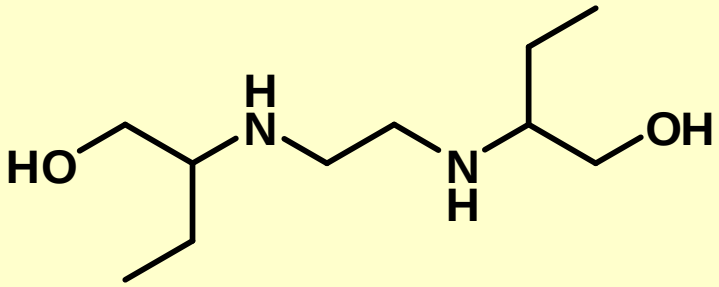
4- Ethambutol (ETB)



(+)-2,2-(Ethylenediimino)di-1-butanol

- **(+)-Isomer of Ethambutol is 200 to 500 times more active than the (-)-isomer. The difference in activity between the isomers suggests a specific receptor for its site of action.**
- **Ethambutol is a water-soluble, bacteriostatic agent readily absorbed (75-80%) following oral administration**

Structure Activity Relationship (SAR):



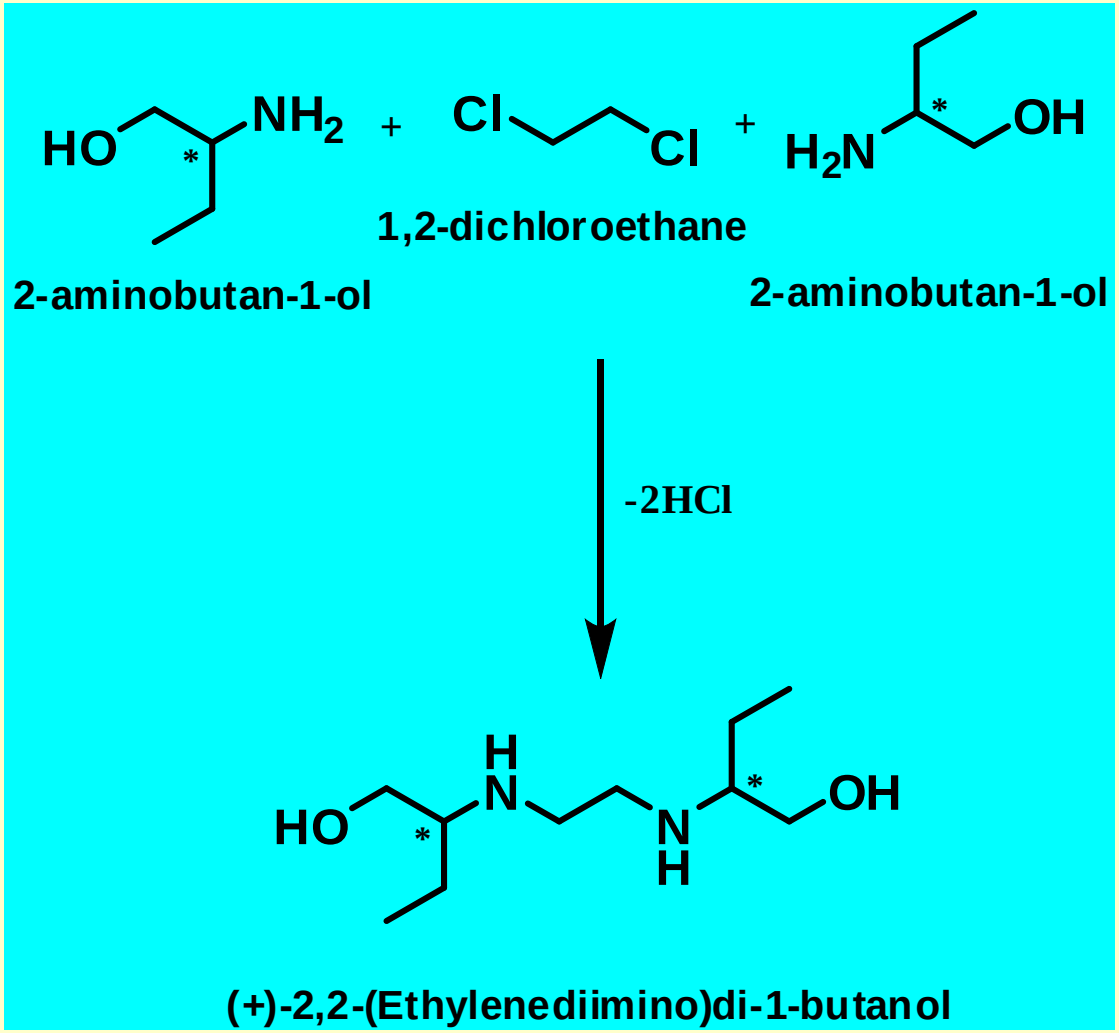
The following changes drastically reduce or even abolish the anti-TB activity:

- **Extension of the ethylenediamine chain,**
- **Replacement of either nitrogen,**
- **Increasing the size of the nitrogen substituent's,**
- **Moving the location of the hydroxyl groups.**

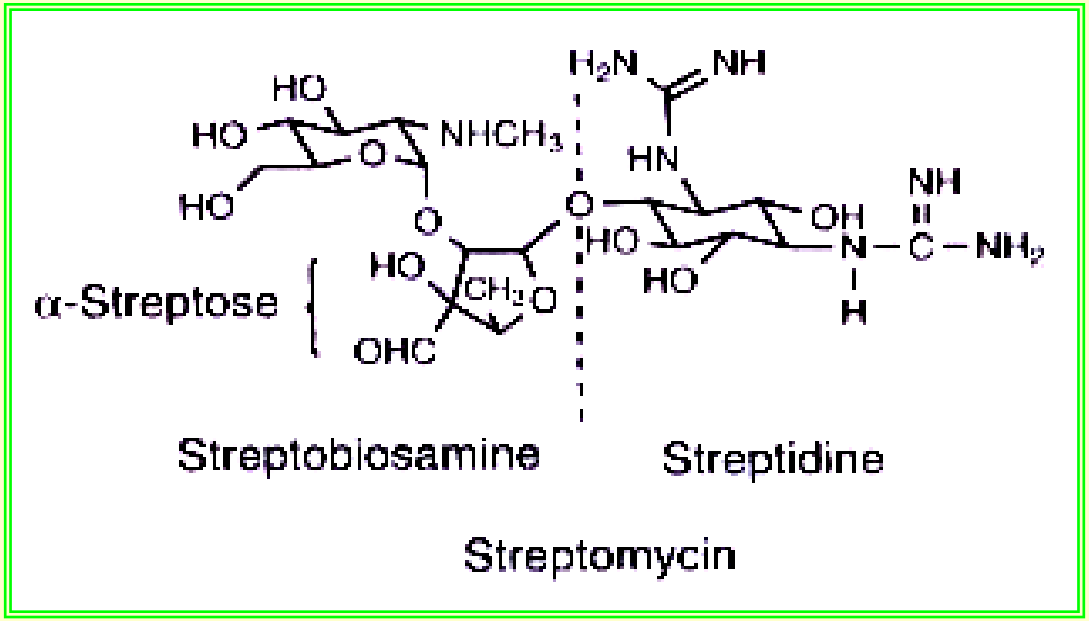
Mode of action:

- **Ethambutol may interferes with cell wall synthesis of *M. tuberculosis* by Inhibiting mycolic acid incorporation.**
- **Ethambutol acts by chelation of metals necessary for the enzymatic activity of *M. tuberculosis*.**

Synthesis:


HO
NH2
*
+
Cl
Cl
1,2-dichloroethane
+
H2N
*
OH
2-aminobutan-1-ol
2-aminobutan-1-ol
-2HCl
HO
*
H
N
N
H
*
OH
(+)-2,2-(Ethylenediimino)di-1-butanol

5- Streptomycin



- **Streptomycin is an aminoglycoside antibiotic produced by *Streptomyces griseus.***
- **The hydrophilic nature of Streptomycin results in a very poor absorption from GIT and lack of biologic activity following oral administration. It is used via I.M. for TB treatment.**

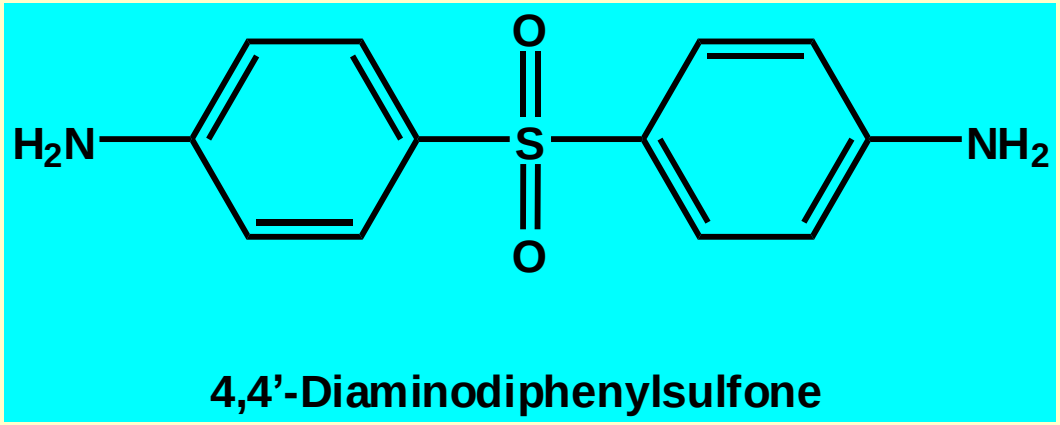
Mode of Action:

- **Binding of Streptomycin to the 30S ribosomal subunit is the primary site of action.**
- **This binding causes disruption of normal protein synthesis, as well as the formation of abnormal protein.**

Antileprotic Drugs

- **Leprosy is a chronic infection affecting skin, mucous membrane and peripheral nerves caused by *Mycobacterium leprae.***
- **Detection of antibody to the organism is an effective diagnostic test.**
- **Sulfones are antibacterial agents exert their effect as competitive inhibitors of PABA incorporation into folic acid.**
- **The parent sulfone, Dapsone, is used widely for all forms of leprosy.**

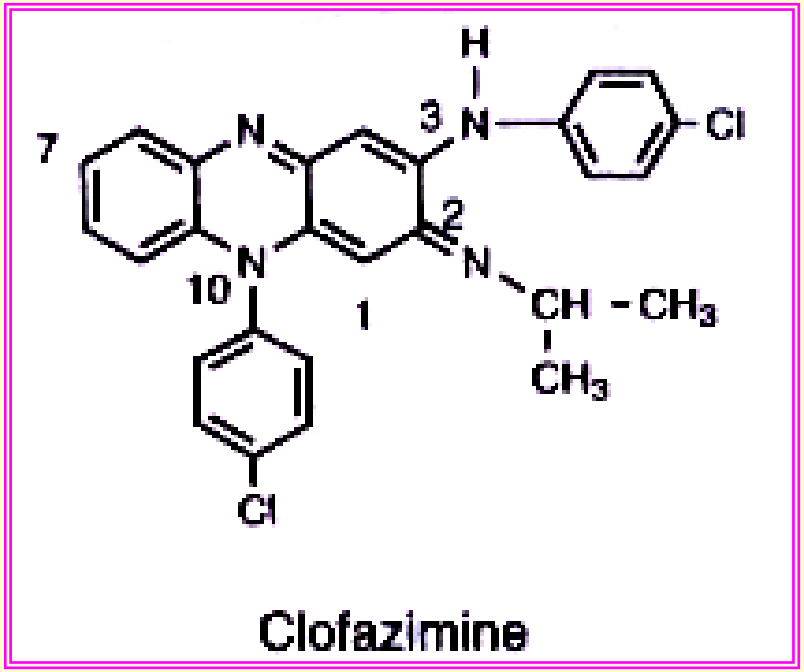
1- Dapsone



4,4'-Diaminodiphenylsulfone

- **Dapsone is the drug of choice even suffering from side effects as hemolytic anemia, and toxic hepatic effects.**
- **Multi-drug therapy is recommended for dapsone-resistant cases; as combination of dapsone with clofazimine and rifampin.**

2- Clofazimine

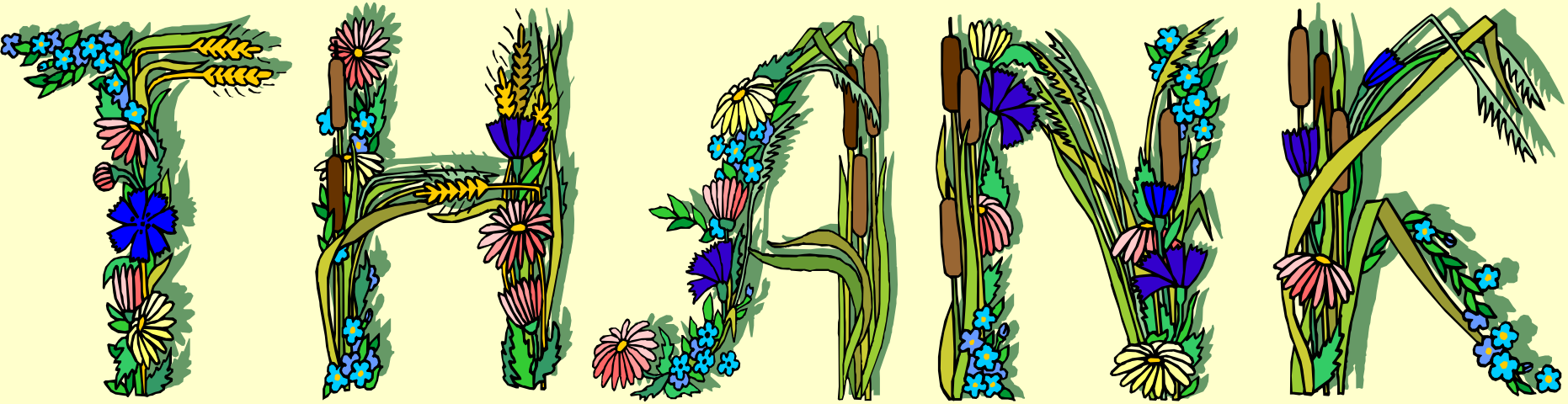


Clofazimine

- **Clofazimine is a phenazine water-insoluble dark red dye that causes skin pigmentation and discoloration of body secretions.**
- **It is classified as a secondary bactericidal drug for treatment of leprosy and commonly used as a component of multiple drug therapy.**

3- Rifampin

- **Rifampin is an antitubercular drug, with actions against *M. leprae* parallel those reported for *M. tuberculosis*.**
- **It is used as an antileprotic agent in combination with the sulfones.**


THANK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